



NTP
National Toxicology Program

Meeting Format & Agenda

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Product: NTP Monograph

- Primary aim is to focus research activities
- NTP literature review + expert input = final chapters
 - Current drafts are NTP literature reviews
 - Experts will review for coverage of the literature, accuracy, and clarity
 - Expert input to provide interpretation and conclusions
 - Consensus not required
 - Documents will be updated after the meeting to incorporate workshop deliberations + electronic review by breakout group members
- Published as an NTP Monograph
 - Target date for finalizing chapters – summer 2011



Overview of Breakout Group (BOG) Sessions

- Charge questions refined to suit each BOG
- Address charge questions using posted draft documents
 - Arsenic; BPA, maternal smoking/nicotine; pesticides, organotins + phthalates
 - Text on “other metals” will be developed and included in final Monograph
 - Arsenic >> cadmium > lead, nickel, mercury
- GR, ER, AR and thyroid hormone session
 - General discussion on role of these hormones in regulating glycemic control and adiposity
 - Frame discussions for BPA and identify other research needs



Tox21 High Throughput Screening

- Collaborative program between the EPA, NIEHS/NTP, NIH Chemical Genomics Center and FDA (<http://epa.gov/ncct/Tox21/>)
 - Includes a variety of assay platforms/technologies
- Tox21 data incorporated into several chapters and sessions
 - Introduce researchers to Tox21
 - Stimulate discussion on how to best assess applications of Tox21 data
 - Use to identify research questions?
 - Help determine biological plausibility of reported effects?
- Identify additional assay targets/technologies for diabetes/obesity



Bioinformatics and High Throughput Screening Breakout Group Sessions

- 1st session – Orientation to Tox21
 - Overview of Tox21, training session on accessing Tox21 data, demo of the “human pathway universe”
- 2nd session – Bioinformatic approaches
 - Agenda change: A bioinformatics approach for identifying assays that query human health effects, Scott Auerbach NIEHS/NTP
 - Environmental wide association study (EWAS) on type II diabetes mellitus (Chirag Patel, Stanford)
- 3rd session
 - HTS profiling for biological processes related to diabetes and obesity
 - Islet cell function, insulin sensitivity, fatty acid metabolism, adipocyte differentiation, feeding behavior, hypertension
 - Identifying other assay targets to consider adding to Tox21



Table 8. Pattern of screening data for Amitraz and other chemicals tested in Phase 1 of ToxCast™ that interacted with same assay targets¹

CASRN	Name	adrenergic receptor, α-2A (ADRA2A)	adrenergic receptor, α-2A (Adra2a)	monoamine oxidase A (NVS ENZ rabi2C)	serotonin receptor 7 (HTR7)	adrenergic receptor, α-2b (Adra2b)	serotonin receptor 1A (Htr1a)
33089-61-1	Amitraz	0.05	0.06	0.16	0.45	1.03	1.8
43222-48-6	Difenzoquat metilsulfate	1.07	3.18	27.1	47.1	0.59	
155569-91-8	Emamectin benzoate	21.3	20.8		4	23.5	
68157-60-8	Forchlorfenuron	22.1	40		48.5		
67747-09-5	Prochloraz		1.83		39.4	4.7	
118134-30-8	Spiroxamine	6.82	29.7		14.4		
119446-68-3	Difenoconazole		2.36			29.5	
76-87-9	Fentin	5.79			0.2		
35554-44-0	Imazalil			42.4		12.4	
87820-88-0	Tralkoxydim	21.8				7.41	
2971-36-0	2,2-Bis(4-hydroxyphenyl)-1,1,1-trichloroethane (HPTE)				8.85		
71751-41-2	Abamectin				4.7		
314-40-9	Bromacil				47.2		
133-06-2	Captan				44.9		
120-32-1	Clorophene				16.5		
210880-92-5	Clothianidin					29.6	
120116-88-3	Cyazofamid					22.7	
52315-07-8	Cypermethrin				42.5		
85509-19-9	Flusilazole				38.8		
23422-53-9	Formetanate hydrochloride			1.94			
79983-71-4	Hexaconazole				41.9		
8018-01-7	Mancozeb		41.3				
51596-11-3	Milbemectin				6.84		

¹Data presented as active concentration (AC₅₀) in μM. Based on assay targets most relevant for effects on glucose control (i.e., excludes whole cell toxicity, genes involved in immune/inflammation)



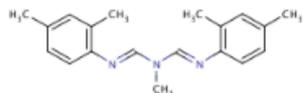
ToxCastDB

You are here: EPA Home » National Center for Computational Toxicology » ToxCastDB » Chemical

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Chemical: Amitraz



CASRN 33089-61-1
Smiles Cc2cc(C)ccc2/N=C/N(C)/C=N/c1ccc(C)cc1C
Source Name SID DSSTOX_40344
Source Name CID DSSTOX_3871
ACToR [Find in ACToR DB](#)

Data

Source	Assay	Assay Name	Species	Gene	Value	Units
ACEA	ACEA_LOC2	ACEA_LOC2	Homo sapiens		33.1	uM
ACEA	ACEA_LOCdec	ACEA_LOCdec	Homo sapiens		33.1	uM
ACEA	ACEA_IC50	ACEA_IC50	Homo sapiens		29.4	uM
BioSeek	BSK_BE3C_hLADR_down	BrEPI_IL_1b_TNF_a_IFN_g_24_HLA_DR_down	Homo sapiens	HLA-DRA	13.3	uM
BioSeek	BSK_BE3C_SRB_down	BrEPI_IL_1b_TNF_a_IFN_g_24_SRB_down	Homo sapiens		40.0	uM
BioSeek	BSK_hDFCGF_VCAM1_down	HDFFn_IL_1b_TNF_a_IFN_g_EGF_FGF_PDGFbb_24_CD106_VCAM_1_down	Homo sapiens	VCAM1	13.3	uM
BioSeek	BSK_hDFCGF_MIG_down	HDFFn_IL_1b_TNF_a_IFN_g_EGF_FGF_PDGFbb_24_CXCL9_MIG_down	Homo sapiens	CXCL9	13.3	uM
BioSeek	BSK_hDFCGF_Col3a1_down	HDFFn_IL_1b_TNF_a_IFN_g_EGF_FGF_PDGFbb_24_Col3a1_down	Homo sapiens	COL3A1	13.3	uM

Table 9. ToxRef search results for chemicals that caused increased body weight (or body weight gain), increased glucose, or pancreatic effects. Those shaded red were tested in Phase 1 of ToxCast™ (hyperlink access data from EPA website, see also Appendix B for screening data + common names for gene-based assay targets)

Chemical and CASRN	Chemical Class	Study Design*	Doses Tested (mg/kg-d)		Effect Doses (mg/kg-d)			Citation
			Lowest	Highest	↑ Body Weight	↑ Glucose	Pancreatic Pathology or Neoplasia	
Cymoxanil (57966-95-7)	aliphatic nitrogen	CHR, rat, feed	1.98	126			126	(Cox 1994b)
Cymoxanil (57966-95-7)	aliphatic nitrogen	CHR, mouse, feed	4.19	582			582	(Cox 1994a)
Acetochlor (34256-82-1)	amide	CHR, rat, feed	0.67	92.1			92.1	(Broadmeadow 1988)
Propyzamide (23950-58-5)	amide	SUB, rat, feed	2.5	289.2			254	(Anderson et al. 1989)
Abamectin (71751-41-2)	antibiotic	CHR, rat, feed	0.7	2.1	0.7			(Gordon 1985)
Emamectin benzoate (155569-91-8)	antibiotic	CHR, rat, feed	0.25	2.55	1.01			(Lankas 1994)
Azoxystrobin (131860-33-8)	antibiotic	SUB, rat, feed	20.4	448.6		223	444	(Milburn 1992)
Dicamba (1918-00-9)	aromatic acid	CHR, rat, feed	2.5	125	125			(Goldenthal 1985)
Quinclorac (84087-01-4)	aromatic acid	CHR, rat, feed	56	757			487	(Schilling 1988)
Ethofumesate (26225-79-6)	benzofuranyl alkylsulfonate	CHR, rat, feed	97	1466		332	1470	(Everett et al. 1991)
Diphenylamine (122-39-4)	bridged diphenyl	SUB, rat, feed	9.6	1323.8		650		(Krohmer 1992)
Carbofuran (1563-66-2)	carbamate	MGR, rat, feed	1	5	1			(EPA)
Sodium Dimethyldithiocarbamate (128-04-1)	carbamate	SUB, rat, gavage/intubation	0.5	250		250	250	(Marquis 1991)
Bifenazate (149877-41-8)	carbazate	CHR, rat, feed	1	9.7	1.2			(Ivett 1999)
Tetraconazole (112281-77-3)	conazole	SUB, rat, feed	0.7	28.7	23.9			(Mayfield et al. 1988b)
Propiconazole (60207-90-1)	conazole	CHR, rat, feed	3.6	100.6			18.1	(Hunter et al. 1982)
Sethoxydim (74051-80-2)	cyclohexene oxime	CHR, mouse, feed	4.48	142.85		4.85		(Takaori et al. 1981)
Tepraloxymid (149979-41-9)	cyclohexene oxime	CHR, rat, feed	5	272			272	(Mellert et al. 1997)
Halofenozide (112226-61-6)	diacylhydrazine	SUB, rat, feed	0.07	54.61		52.7		(Anderson et al. 1995)
Captafol (2425-06-1)	dicarboximide	SUB, rat, feed	174	174	174			(Brorby 1986)
Imazalil (35554-44-0)	imidazole	SUB, rat, feed	1.25	60		3.75		(Lina et al. 1983)
Disulfoton (298-04-4)	organophosphorus	CHR, mouse, feed	0.15	2.4	2.4			(Mobay Chemical Corp. 1983)
Malathion (121-75-5)	organophosphorus	CHR, rat, feed	4	868			29	(Daly 1996)
Parathion-methyl (298-00-0)	organophosphorus	CHR, mouse, feed	0.2	13.7	9.2			(Eiben 1991)
Propetamphos (31218-83-4)	organophosphorus	CHR, rat, feed	0.376	7.602			0.689, 7.6 (n)	(Luginbuehl 1980)
Tebupirimfos (96182-53-5)	organophosphorus	CHR, mouse, feed	0.52	43.57	38.8	38.8		(Eiben 1990)
Tebupirimfos (96182-53-5)	organophosphorus	SUB, rat, feed	0.2	4.9		0.4		(Eiben 1989)
Tribufos (78-48-8)	organophosphorus	CHR, mouse, feed	1.64	63.04	48			(Hayes 1989)

*CHR = chronic; SUB = subchronic; MGR = multigenerational study



POPs – Forest Plot Generator Software and Database

- Complex literature, many human studies
- Needed expert input prior to developing text-based chapter
 - ~50 page table of study summaries, ~500 main results
 - Too large of a literature to look for patterns in text-based format
- Developed software to display graphically (“Forest Plot Generator”) as a tool
 - Developed by Shawn Harris, SRA International



Forest Plot Program cont.

- POPs BOG will use forest plot program as a tool in their deliberations
 - Values in blue in appendix table added to forest plot database
 - Diabetes, glucose, insulin, metabolic syndrome, developmental exposure + growth later in life
- Forest Plot software program + excel data file can be provided upon request
 - thayer@niehs.nih.gov; 919-541-5021



QUESTIONS?